Exhibit K

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RESEARCH HIGHLIGHT

The significance of testosterone for fair participation of the female sex in competitive sports

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Sex segregation in competitive sports is regarded as fair. Before puberty, boys and girls hardly differ in height, muscle and bone mass. Pubertal testosterone exposure leads to an ultimate average greater height in men of 12–15 centimeters, larger bones, greater muscle mass, increased strength and higher hemoglobin levels. Post-pubertal androgen ablation reverses, at least in part, previous anabolic effects of testosterone on muscle,[1] bone mineral density and hemoglobin, but the bones remain longer and have a wider diameter. As testosterone administration produces a dose-dependent increase in muscle mass and maximal voluntary strength,[2,3] exogenous androgens are banned as performance-enhancing drugs.[4] Men with testosterone deficiency are allowed to receive testosterone replacements which do not raise blood testosterone levels above the normal male range.[5,6]

A recent paper highlights the historical case of a Dutch female athlete (1926–2007) outperforming most of her competitors in the years 1948–1950.[7] DNA analysis revealed that she was 46,XX/46,XY mosaic, with equal numbers of both genetic cell types. While having breasts, she also had a degree of facial hairiness pointing to an excess of circulating testosterone, likely produced by the presence of Leydig cell in her gonads on the basis of her XX/XY mosaicism. On the basis of this case, the authors have also given attention to the societal context of sports women becoming involved in a (public) discussion about their sex which is an intrusion into their privacy. The authors advocate that matters of sex of participants in competitive sports should be settled before athletes enter the arena, and this will be elaborated below.

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Prior to the year 2000, genotyping was the means of determining sex for competition in sports. Chromosomal sex alone is not a particularly adequate indicator for the purpose of ensuring fair competition, however. In humans, there is no solid evidence that the pattern of sex chromosomes has a direct effect on muscle mass and strength. Rather, the influence is indirect through determination of the nature of the embryonic gonadal anlagen (testes or ovaries), the hormonal products of these (testosterone and estradiol) and the quantitative relationship between those products. In sports, previous and present exposure to androgens is a reasonable criterion for reducing unfair competition, for both women and men. So, previous and present exposure to testosterone should be the determinant of fair competition between men and between women, also separating the two sexes. Changes in fat-free mass, muscle size, strength and power appear to be associated with testosterone dose and achieved concentrations.[8]

An issue is the participation in competitive sports of people with errors of sexual differentiation and also of transsexuals treated with cross-sex hormones (i.e., female-to-male transsexuals receiving doses of testosterone similar in magnitude as men receiving testosterone replacement). With regard to the effects of testosterone in transsexuals, the dividing line is whether sex (re)assignment has taken place before or after hormonal puberty. Before puberty, there are no significant differences in body composition between girls and boys, so, in this context only post-pubertal sex reassignment is relevant.

It has been demonstrated in the rat that genetic configuration and gonadal status have no known significant effect on sensitivity to the biological action of sex steroids.[9] Effects of testosterone in puberty and thereafter are certainly in part reversible but there is no definitive information on the extent of this. It is unknown whether or for how long earlier effects of androgen exposure carry over after androgen ablation.[10] In a study comparing muscle surface areas between male-to-female transsexuals and female-to-male transsexuals, we noted a significant difference in the average, but there was also a considerable overlap between the two groups before any hormonal intervention had taken place. In spite of muscle surface area reduction induced by androgen deprivation, after 1 year the mean muscle surface area in male-to-female transsexuals remained significantly greater than in untreated female-to-male transsexuals; again, an almost complete overlap was noted between the two groups. Testosterone administration to female-to-male transsexuals increased muscle surface areas significantly, producing a large overlap with untreated male-to-female transsexuals but with a significantly lower mean.[10] Effects of cross-sex hormones on insulin-like growth factor and hemoglobin levels paralleled changes in muscle surface area.[10]

Another group of interest is subjects with disorders of sexual differentiation and other subjects with a higher-than-normal endogenous production of androgenic–anabolic hormones (such as congenital virilizing adrenal hyperplasia and polycystic ovarian syndrome). There are studies reporting a higher lean body mass and bone mass in women with polycystic ovarian syndrome,[11–13] but whether this translates into better performance in sports is unknown.

For transsexual people, the International Olympic Committee has drawn a necessarily arbitrary but reasonable line with regard to participation of sex-reassigned transsexuals: sex reassignment must have taken place at least 2 years earlier. In support of this decision, in the abovementioned study, we found that changes in muscle surface area

were not greater after 3 years of cross-sex hormone administration than after 1 year.[10] Hormone treatment must be appropriate for the reassigned sex (no overdosing of testosterone in female-to-male transsexuals), and the reassigned sex must be legally recognized. The International Olympic Committee policy is not binding for other sports organizations. Very recently (1 May 2011), the International Association of Athletics Federations (IAAF) has adopted revised guidelines for the participation in sports of athletes who have undergone sex reassignment. Reassigned transsexuals must notify the IAAF of their status if they wish to compete with others. This will be dealt with confidentially for the protection of the privacy of the person, thus avoiding public debate on the sex of the participant. The person in question will be examined by an Expert Medical Panel of the IAAF assessing the period of time since the sex reassignment, the athlete's androgen levels and the nature, duration and results of any treatment following sex reassignment. The results will be reported to the IAAF which will grant permission if the medical assessment does not provide indications of unfair advantage over other female competitors.

For subjects with hyperandrogenism, on 12 April 2011, the IAAF announced the adoption of new rules and regulations governing the eligibility of females with hyperandrogenism to participate in women's competition, which equally have come into force on 1 May 2011 (http://www.iaaf.org/aboutiaaf/news/newsid=59746.html). The approach is similar to that of transsexuals. Athletes with a hyperandrogenic disorder report to the IAAF and will undergo an assessment by the Expert Medical Panel. The IAAF is of the opinion that elevated androgen levels originating from congenital virilizing adrenal hyperplasia or polycystic ovarian syndrome or similar conditions are no ground for exclusion even though the associated hyperandrogenism may provide some advantages to the athlete. For the time being, the upper limit of acceptable serum testosterone levels is a level that is clearly at the lower limit of the normal male range (10 nmol l^{-1}). This position was adopted because there is no consensus on the upper range of serum testosterone levels in women,[14] also in view of the problems with accurate measurements, metabolites, circadian rhythm and binding proteins etcetera of serum testosterone.[15] The present upper limit of acceptable serum testosterone levels seems a compromise of a committee that had to come up with formal rules generally applicable to a population of female athletes. It might very well be that future medical research solves the problems of determining one's androgen status more accurately and that a stricter consensus can be reached what constitutes hyperandrogenism in women. If so, it is likely that the upper limit of acceptable androgen levels for female athletes will be lowered. Most practicing physicians will start diagnostic work-up of hyperandrogenism if serum testosterone exceeds 3–5 nmol l^{-1}.

Eventually, it is illusionary to arrive at 100% fairness in competition on the basis of serum testosterone levels. First of all, there are the well-known methodological difficulties of measuring serum testosterone levels reliably.[15] Second, serum testosterone levels provide an indicator of the strength of the androgen signal, but have limited predictive value of the biological effects of testosterone which are codetermined by properties of the androgen receptor.[16] This is exemplified in people with abnormalities of the androgen receptor who have high circulating serum androgen levels, but androgen action is impaired due to genetically determined abnormalities of the molecular properties of the androgen receptor (androgen insensitivity syndrome). It seems further appropriate to place the effects of testosterone in the perspective of naturally occurring and imponderable differences in sporting capability between members of the same sex. Unfair competition should be prevented as much as possible, and the above measures of the IAAF are the best possible at present, but ultimately Nature is unfair in her endowments of talents for all walks of life, including sports.

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